
Immunology

JAN KLEIN

Max-Planck-Institut für Biologie

Tübingen

Federal Republic of Germany

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and generalized swelling. Some of the affected fetuses may be aborted, others may be delivered stillborn, and others still may be born alive but with severe defects, particularly in the central nervous system, where considerable damage is caused by the deposit of bilirubin in ganglia. Haemolytic disease of the newborn does not always develop in a Rh⁻ mother carrying an Rh⁺ fetus. Usually the first pregnancy is not affected, but in later pregnancies, as the titre of Rh antibodies increases, the chances of haemolytic disease of the newborn also increase. The disease can be prevented by giving the mother anti-RhD IgG fraction intramuscularly at the time of delivery (within 60 h). These passively administered antibodies prevent sensitization of the mother's lymphoid system and thus the production of RhD antibodies. The passively administered antibodies are then eliminated by natural decay. This treatment reduces the risk of an anamnestic response during subsequent pregnancies by 95%.

Type III hypersensitivities induced by immune complexes

Principle

The interaction of antigens with their corresponding circulating antibodies leads to the formation of *antigen-antibody (immune) complexes*. Normally, immune complexes are removed from the circulation through the mononuclear phagocyte (reticuloendothelial) system, particularly in the liver (by Kupffer cells), spleen, and lungs, but if they are formed in large quantities, they are deposited in various tissues. The deposited immune complexes bind and activate complement and the C3a and C5a fragments so generated bind to basophils in the blood and cause their degranulation. Immune complexes may also interact directly with basophils and platelets (the immunoglobulin Fc regions) and cause their degranulation. Some of the released mediators, in particular histamine and 5-hydroxytryptamine, cause retraction of endothelial cells and so increase the permeability of the blood vessels and lead consequently to the deposit of more immune complexes. The activated platelets aggregate and initiate the formation of small clots on the collagen of the exposed basement membrane beneath the endothelial cells. Other mediators attract neutrophils which then attempt to phagocytose the deposited complexes. The tissue-bound complexes cannot be easily engulfed, however, and the macrophages spill their

lysosomal contents over the tissue. Normally, the released lysosomal enzymes would be inactivated quickly by substances in the serum, but since the serum is to a great extent excluded from the contact zone between the phagocytes and the tissue cells, they have enough time to attack the tissue. The resulting tissue damage leads to a form of hypersensitivity which involves IgG rather than IgE antibodies. The hypersensitivity manifests itself in a characteristic tissue response which will be described shortly.

The immune complexes are deposited preferentially in certain sites throughout the body — the kidney glomerulus, the joints, the lungs, and the skin. The reasons for this preference may vary from organ to organ. The deposit of immune complexes in the kidney may occur because the blood pressure in the glomerular capillaries is four times higher than in other capillaries. Also, the glomerulus is a filter through which body fluids have to pass and it may retain immune complexes by a simple filtering effect. For a similar reason, immune complexes may also accumulate on other body filters: the ciliary body of the eye, where aqueous humour forms, and the choroid plexus in the brain, where cerebrospinal fluid is produced. The characteristics of the disease which leads to immune-complex deposits may also determine the site for the deposit. Systemic lupus erythematosus, for example, is characterized by the appearance of DNA-specific antibodies (see Chapter 24) and since DNA has affinity for collagen in the basement membrane of the glomerulus, most of the DNA-anti-DNA complexes accumulate in this organ. Another example is rheumatoid arthritis, in which plasma cells produce Ig-specific antibodies in the synovium of the joint and the immune complexes thus initiate an inflammatory response at this site. Why the deposition of immune complexes only occurs in certain diseases is not known. Possible contributory factors include the affinity of the antibodies and the valency of the antigen (low-affinity antibodies combining with low-valency antigens may form complexes that the body has difficulty clearing); the participation of complement (binding of C3b and C3d to immune complexes solubilizes deposited complexes and the lack of appropriate complement involvement may have the opposite effect); and the nature of the antigen, as was pointed out earlier.

Immune complexes form frequently in autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis. The other two situations in which immune complexes may be

involved in the pathogenesis of the disease are, first, low-grade persistent infections such as those characterizing leprosy, malaria, African trypanosomiasis, and viral hepatitis; and second, repeated exposure of body surfaces, such as the lungs, to antigenic material such as pigeon antigens (leading to *pigeon fancier's disease*), or fungi from mouldy hay (leading to *farmer's lung disease*). The experimental models of these two situations are the Arthus reaction and serum sickness.

Arthus reaction

In 1903, N. Maurice Arthus and Maurice Breton described an experiment in which they repeatedly injected normal horse serum subcutaneously into rabbits, with an interval of several days between the individual injections. After the fifth or sixth injection, they observed a skin reaction characterized by firm induration, swelling, abscess formation, and eventual necrosis. It was not necessary that the site of the last injection coincided with that of previous injections; the reaction could be observed at any site where the last injection was made. The phenomenon, now referred to as the *Arthus reaction*, is not peculiar to rabbits; similar reactions were also observed in guinea-pigs, rats, dogs, and humans. The reaction is explained as follows (Fig. 21.17). The repeated injections induce

the formation of precipitating antibodies specific for horse proteins. As the antigen diffuses from the injection site through the tissue and into the regional blood vessels, it combines with the antibodies and insoluble antigen-antibody complexes form locally in the venules. The immune complexes are deposited between and beneath the endothelial cells, where they activate complement. The chemotactic factors liberated from the complement cascade begin to attract neutrophils and platelets to the reaction site. The neutrophils adhere to the tissue-bound immune complexes via their C3 receptors (CR1) and attempt to phagocytose them. Since, however, the complexes are attached to a nonphagocytosable substrate (the basement membrane), the phagocytosis is incomplete and the phagolysosome remains open to the exterior, releasing lysosomal enzymes into the surrounding medium. The released enzymes attack the basement membrane and the tissue surrounding it, collagenases disrupting collagen fibres, neutral proteases destroying the ground substance, and elastases degrading elastic fibres. The proteases also generate C5a from C5, which initiates degranulation of the neutrophils. The mediators released from the granules promote further neutrophil accumulation and degranulation. Some of the mediators act on mast cells and basophils causing their degranulation, thus further exacerbating the inflammatory reaction. Some of the

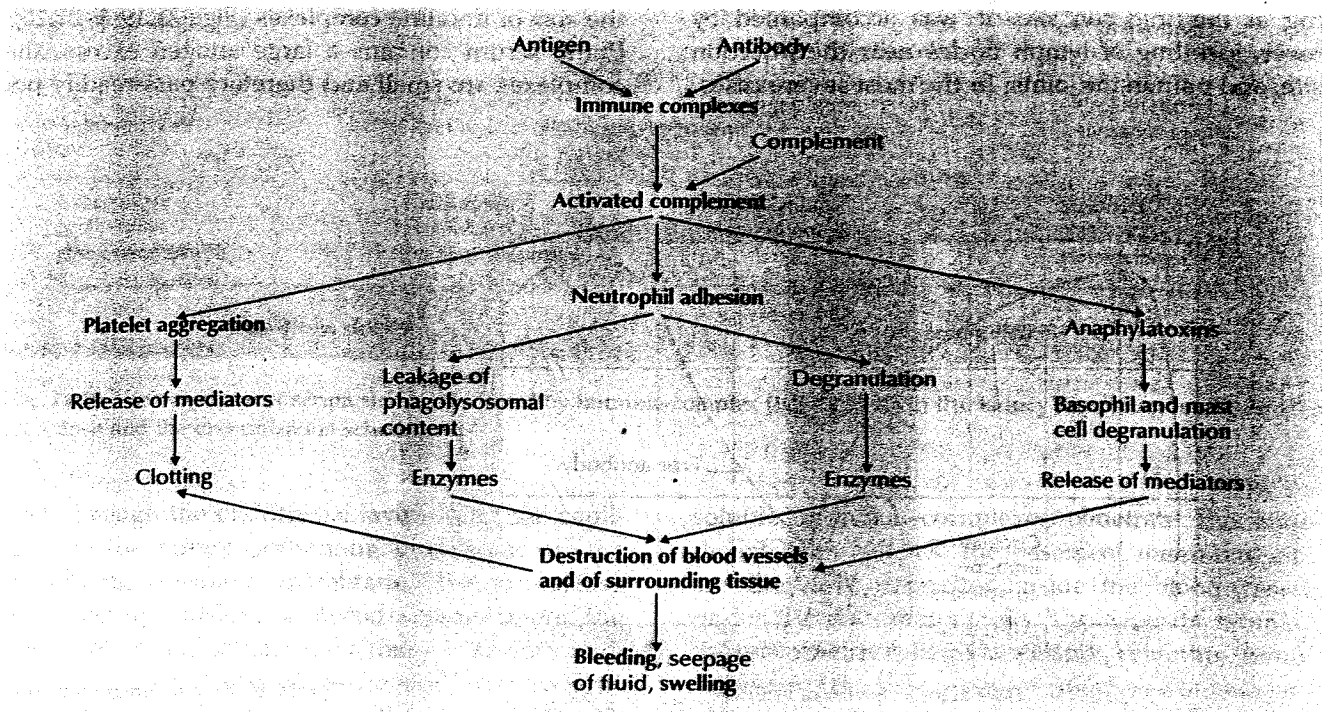


Fig. 21.17 Major mechanisms leading to the Arthus reaction.